

OBSERVATIONS ON SERUM DISEASE.

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I N T R O D U C T I O N .

The observations which form the basis of this work were made from upwards of 200 cases which developed the phenomena of "serum disease" or otherwise certain sequelae following serum injection - a condition which is intimately allied to super-sensitiveness. The real factor is the introduction of foreign protein into the human tissues.

Lublinski¹ (1894) noted that injections of anti-toxin were sometimes followed after a few days by a train of symptoms which are now termed "Serum disease". The principal symptoms then noted were rash, temperature and pain in the joints. The disease is now most common following the administration of antidiphtheritic serum but when serum treatment was extended to include antistreptococcal and antitetanic serum it was found that the phenomena was not due to the antitoxic part in the serum but to the serum itself or the protein non-antitoxic part of the serum.

The clinical features according to Von Pirquet and Shiek² are.-

- (1) The development of the serum rash which is the first indication and spreads from the site of injection over the rest of the body.

- (2) Temperature and quickened pulse rate.
- (3) Arthritis - (a most prominent symptom).
- (4) Enlargement of the lymphatic glands.
- (5) Oedema of the subcutaneous tissues.

But in addition to those mentioned by the above named observers, there may be vomiting and often a slight patching of the fauces and as we shall see later, marked changes in the blood picture, principally the white corpuscles.

Von Pirquet and Shiek also describe an immediate and an accelerated reaction. An immediate reaction is seen when a large dose has been given and a second dose administered; the interval is usually from twelve days to eight weeks, though often as long as six months. The symptoms of the immediate reaction are intense local oedema, general exanthemata and pyrexia. The symptoms pass off usually within 24 hours. The accelerated reaction is also seen after the second injection and it may occur from six weeks up to many months after the first injection. In the accelerated reaction there is an incubation period, but shorter than in the case of the first injection, usually from five to seven days. The symptoms resemble those in the ordinary reaction already described but have a rather more acute onset and last a shorter time.

In/

In the interval from about the sixth week to the sixth month there may occur both the immediate reaction and also a few days later an accelerated reaction.

As we shall see later, the symptoms of the immediate or the accelerated reaction are essentially the same as those of anaphylactic shock but differ only in the degree of intensity.

OBSERVATIONS AND GENERAL ANALYSIS OF SERUM RASHES.

Serum rashes occurred in 25% of the total patients under observation, that received an injection of antitoxin. Of these cases 9% showed accelerated reactions, that is, cases that received serum on previous occasions. This had an effect of shortening the incubation period and gave rise to more rapid and acute symptoms than in the others. The rashes produced are of various kinds and are divided by Ker³ into four main groups, namely:-

- (1) Multiform erythema.
- (2) Urticarial.
- (3) Morbilliform.
- (4) Scarlatiniform.

TABLE I.

<u>Type.</u>	<u>Number.</u>	<u>Percentage.</u>
Multiform Erythema	94	44.5
Urticarial	66	31.2
Morbilliform	33	15.5
Scarlatiniform	<u>17</u>	<u>8.8</u>
Totals.	210.	100.0

With regard to the clinical differences of the rashes, the "Multiform erythematous" rash appears as an irregularly blotched rash, of a bluish pink colour, in places almost morbilliform, in others erythematous. They often tend to become circinate while elsewhere they may present longitudinal looking patches without the characteristic wheals. As compared to the other types they occur most frequently of all. Table I shows their order of occurrence to be 44.5%. The usual site of this multiform rash is over the knees, elbows, inner side of thighs, back, and spreading to the face and arms. There is a certain amount of a smarting sensation and sometimes oedema of the extremities and puffiness of the face.

The "urticarial" rash appears suddenly with typical wheals, red blotches irregular in shape and scattered, usually affecting the region about the site of the injection. In some cases the wheal formation is not definitely seen but the resemblance to urticaria still remains; the appearance of the wheals on the whole varies, they are firm to the touch and about the size of a shilling, rather oval shaped. There is often oedema around the wheals.

The eruption disappears very quickly and leaves a slight transient hyperaemia. The irritation and itching/

itching is intense, more so than in any of the other rashes. Table I shows their frequency of occurrence to be 31.2%.

The "Morbilliform" rash consists of macules, reddish in colour and smaller than those of measles and not so raised. Usually begins about the site of the injection and spreads to the face, trunk and extensor surfaces of the extremities. Except for the complete absence of coryza it may be taken for measles but of course there are no Koplick spots. The irritation is not nearly so marked as in the urticarial type. Table I shows the frequency of occurrence of the morbilliform type to be 15.5%.

The "Scarlatiniform" type, the last to be described, gives the greatest trouble in diagnosis as there is a strong resemblance to scarlet fever. There is irritation usually with no constitutional disturbance and the tongue and throat are atypical of scarlet fever. The punctate erythema is sometimes observed first in the neighbourhood of the site of the injection. Table I in the case of the scarlatiniform type shows the frequency to be 8.8%.

Like other fevers there is a definite incubation period from the time of injection of the serum till the clinical manifestation of the serum disease.

TABLE II.

Number of days after injection of serum.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	Totals.
Multiform	-	-	-	1	2	9	8	11	19	21	15	4	-	2	2	-	-	-	-	-	-	94
Urticarial	-	-	-	2	5	8	13	13	15	6	2	-	2	-	-	-	-	-	-	-	-	66
Morbilloform	-	-	-	-	-	-	-	2	4	-	11	7	6	2	-	-	-	-	-	-	1	33
Scarlatiform	1	5	7	2	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	17
																						210.

Multiform 6 - 11th day 88.5%

Urticarial 6 - 9th day 75.5%

Morbilloform 11 - 13th day 72.6%

Scarlatiform 2 - 4th day 82%

The earliest appearance of a serum rash was a quarter of an hour after an injection but this appears to be exceptional and was only noted in one case, - one of a scarlatiniform type. The latest appearance of a rash was on the 21st day - again exceptional. In this case there were two rashes, the morbilliform being preceded by an urticarial one.

The foregoing table shows that the number of rashes increases as the incubation period lengthens. Taken on the whole the majority have an incubation period of 6 to 13 days unless the scarlatiniform, which have a maximum number between the 2nd and 4th days; and it was also noted with this type of rash that the erythema first appeared around the site of the injection.

The order of occurrence of incubation periods is thus, scarlatiniform first 2 - 4 days; urticarial second 7 - 9 days; multiform next 9 - 11 days and lastly morbilliform 11 - 13 days, the scarlatiniform type showing the minimum and the morbilliform the maximum time of appearance.

TABLE III./

TABLE III.

Number of days.

	1	2	3	4	5	6	7	8	9	Totals.
Multiform	23	42	19	7	2	-	-	1	-	94
Urticarial	32	11	13	7	-	3	-	-	-	66
Morbilliform	-	9	9	-	5	-	3	4	3	33
Scarlatiniform	12	3	-	2	-	-	-	-	-	17

Multiform 49% on the 2nd day

Urticarial 50% on the 1st day

Morbilliform 29% on the 2nd and 3rd days
respectively

Scarlatiniform 70% on the 1st day.

With regard to the duration of rashes it will be noted from statistical table III that 49% of the multiform erythematous rashes lasted two days, 24.5% lasted one day only, and the largest duration of a rash of this type was eight days.

The urticarial rashes on the other hand shows that 50% lasted one day only, and the longest duration was six days only.

The morbilliform rashes shows 29% on the second and third days respectively and the longest duration was nine days.

The scarlatiniform shows 70% on the first day, and the longest duration four days.

It/

It is thus apparent that the urticarial and scarlatiniform are of shorter duration than of the other two types and the morbilliform type has the longest duration of all.

In dealing with the other clinical features of the disease Ker⁴ states that pyrexia is one of the most frequent symptoms, and, in fact, may occur without other symptoms, although it usually accompanies joint pains and the rash.

TABLE IV.

	Multi- form.	Urti- carial.	Morbilli- form.	Scarlatini- form.
Temperature	71	32	27	5
No Temperature	23	34	6	12

Table IV thus shows that pyrexia is commonest with the morbilliform type occurring in 81.6% of the cases. The next in order of frequency is the multiform variety which shows percentage of 75.5%. Then the urticarial showing 48.4% and lastly the scarlatiniform with 29.2% of cases with pyrexia.

It is thus seen that the morbilliform and multiform varieties have a larger percentage of pyrexia than the urticarial and scarlatiniform types. Taking into/

into consideration also that morbilliform and multi-form rashes showed a longer duration of rash there is thus a relationship to the duration of the rash and the temperature and in fact the severity of the different types.

TABLE V.

Arthritis.

Multiform	12
Urticarial	6
Morbilliform	18
Scarlatiniform	Nil.

Total 36. Percentage 18%

Arthritis has been noted alone but it is usually in connection with the rash. Table V shows that it occurred in 36 of the 210 cases, or 18%. The table also shows that it is most frequently present with the morbilliform type, next in order of frequency with the multiform, and lastly with the urticarial. There were no cases of arthritis noted in those cases showing scarlatiniform rashes.

Von Pirquet and Shiek are of opinion that it is a most prominent symptom so as only 18% of the total cases under observation had arthritis yet it is quite possible/

possible to be overlooked in cases of very young children, and that may cause a possible error. The joints usually affected are the wrists and ankles and finger joints; sometimes the knee and elbow, shoulder and hip joints. There is not much swelling but a good deal of pain on movement. The pain is not alleviated by the ordinary antirheumatic treatment.

Glandular enlargement was also noted but only in 3% of the total cases and in each case the rash was of the morbilliform variety.

Oedema is slight, affecting the face chiefly. It is transient. It was noted only in 4 cases - 3 were morbilliform types and 1 was a multiform type. No albumin was found on examination of the urine. Ker states that albuminuria has no relation to serum disease.

Vomiting and malaise was noted in a great number of cases, it was rather difficult to make statistics of this symptom. In fact the majority of the severe cases suffered from malaise to a certain extent but vomiting on the whole was rare, and was not noted to occur in any special variety.

Ker also mentions patching of the fauces as a clinical feature occasionally, but again I found it difficult to give a statistical table of this feature.

All/

All the above facts and observations show that the morbilliform and multiform types are the severest, the urticarial next, and lastly the scarlatiniform.

A note may be added about the scarlatiniform type, which many observers deny exists. They state that in all probability these cases are those of a mild unrecognised type of scarlet fever as they often present no constitutional symptoms and they account for the absence of desquamation by the fact that in consequence of the transient nature of the rash that it may be small in amount or of a powdery variety and not noticed. But there is undoubtedly a scarlatiniform type of serum rash although they are apt to appear soon after the administration of the serum and also the fact that the punctate erythema is often observed first in the neighbourhood of the injection, is strongly indicative.

A note on the three cases which developed two rashes is also necessary. In all cases the primary rash disappeared before the second rash appeared. In two of the cases it was noted that the first rash was an urticarial one and the second one a multiform. The other case had a primary urticarial rash also, but developed a morbilliform type as the second rash. The urticarial rash in all the cases was transient and all the constitutional symptoms occurred with the second/

second rash. Von Pirquet and Shiek and Goodall⁵ state that the urticarial precedes the multiform. Goodall's explanation of the occurrence of more than one rash in a single case is due to the mixing of the sera of two or more horses, and he accounts for the character of the rash largely to the idiosyncrasy of the horse. He also states that different sera will produce different sera phenomena. Ker also states that the serum drawn from certain horses is more liable to cause serum disease than others.

It is thus seen that the four types of serum rashes differ in their clinical feature, incubation periods, duration of rash, frequency of occurrence and order of occurrence, and this tends to point to a different causal factor of each type.

THE BLOOD PICTURE IN SERUM DISEASE.

A careful search of the literature elicits no information on this subject and therefore the statistical figures are of considerable interest in the study of the disease.

TABLE VI.

Numbers and percentage of cases
showing a leucopenia.

	Numbers	Percentage.
Multiform	73	75.5%
Urticarial	27	40.8%
Morbilliform	24	72.7%
Scarlatiniform	3	17.6%

The principal interest lies in the white cells of the blood and on making blood counts of the cases a leucopenia of anything from 5000 to 7000 was the chief feature noted. Table VI shows that the largest number of cases presenting a leucopenia was of the multiform and morbilliform varieties. A leucopenia was observed in 75.5% of cases of the multiform type and 72.7% of the morbilliform type. With the urticarial/

urticarial type leucopenia was not such a prominent feature and was noted in 40.8% of cases only. The scarlatiniform variety on the other hand presented a remarkably small percentage of cases with a leucopenia only 17.6%.

Leucopenia occurring in the multiform and morbilliform varieties was much more severe than in the urticarial and scarlatiniform varieties where a white count of from 5000 to 6000 was observed in contrast to 6000 and above in the urticarial. A glance at Table VII will show this.

TABLE VII.

	<u>Leucopenia.</u>			
	4000 - 5000	5000 - 6000	6000 - 7000	7000 -
Multiform	9	41	15	8
Urticarial	-	9	13	5
Morbilliform	3	15	6	-
Scarlatiniform	-	-	1	2
Multiform showing leucopenia between 4000-5000				56.2%
Urticarial " " " "				33.3%
Morbilliform " " " "				62.4%
Scarlatiniform " " "				Nil.

Only/

Only in 12 cases was there a leucopenia lower than 5000. In 9 of the 12 cases the rash was of the multiform type while in 3 cases it was of the morbilliform type. The most marked case of leucopenia was in a case of the morbilliform variety which showed a leucopenia of 4400.

Blood counts were made from the cases the day the rash first appeared, which is really the time of the maximum intensity of the illness. In many of the cases blood counts were made immediately after the rash and the other symptoms had disappeared and it was observed that the number of white cells in the blood very quickly returned to normal. In 3 cases of the morbilliform variety and in 2 cases of the multiform a leucopenia was observed to persist for a longer time-5 days in 2 of the morbilliform type and 3 in the other and 1 day in one of the multiform type and 6 in the other.

Blood films were made from a great many of the cases in which there was a leucopenia, and it was observed that the relative proportion of the white cells was greatly disturbed. A definite increase in the proportion of lymphocytes to polymorpho-nuclear leucocytes was observed; the relative proportion being anything from 35 - 55% of lymphocytes (large and small).

Blood/

Blood films were made and a differential white count done from 75 cases showing the leucopenia (28 cases of the multiform variety, 14 of the urticarial, 26 of the morbilliform and 7 of the scarlatiniform).

TABLE VIII.

Relative increase in lymphocytes
to 35-55%

Multiform	22	83.6%
Urticarial	6	44.4%
Morbilliform	20	88.2%
Scarlatiniform	1	20%

The last figure can scarcely be taken to give an accurate percentage as it was only observed in the one case out of the seven. This Table undoubtedly shows that the proportion of lymphocytes to polymorphs is much more disturbed in the multiform and morbilliform types; and as it was noted in Table VII that a leucopenia was more severe in these two types it is inferred that the more severe the leucopenia, the greater is the disturbance of the balance between lymphocytes and polymorphs.

In 3 of the above cases a definite increase in the proportion of eosinophils was noted. Two of those cases/

cases were of the morbilliform variety and one of the multiform. On inquiring into the history of those three cases it was found that they were all subject to asthma; so this must be taken as the explanation until further investigations can be made.

The explanations of this disturbance of the equilibrium of lymphocytes and polymorphs can be looked upon as the results of certain reactions on the part of the blood forming tissues produced by the actions of certain toxic substances either due to the action of the proteins of the horse serum or by certain poisons generated by perverted metabolic processes within the tissues and organs of the patient himself.

This reasoning is, of course, purely theoretical and it is rather difficult to see how the theory can be substantiated by experiment, so it is possible that the theory remains true.

AN INVESTIGATION INTO THE ANAPHYLACTIC REACTIONS
OF THE PROTEINS OF HORSE SERUM.

In the introduction mention was made of the fact that serum disease was closely allied to anaphylaxis. Richet⁶ says that the symptoms of each are directly comparable. He firstly used the word to mean a function which certain poisons possessed of increasing instead of diminishing the sensitivity of an organism to their action. The symptoms of anaphylaxis in animals which follow immediately after a second injection of the substance are fainting, asphyxia and death, and although those symptoms do not follow on a second injection of serum, yet they may sometimes, and with fatal results. This is termed anaphylactic shock. Those symptoms are much more severe than those which occur in serum disease, yet they are essentially the same and only differ in the degree of intensity.

There is thus a strongly marked supersensitive-ness to an injection of horse serum and as we shall now see, a stronger marked supersensitiveness to one type/

type of horse serum or separated proteins of horse serum than to another, which really means that the serum of certain horses are more liable to cause a serum disease than the serum of other horses.

According to Starling⁷ the proteins of serum are divided into two groups - serum albumin and serum globulin and by fractional precipitation of serum with ammonium sulphate two globulin factors can be obtained - a euglobulin and a pseudo-globulin.

Ledingham⁸ has shown by experiments that the euglobulin part exhibited the maximum anaphylactic activity, the albumin being inert and the pseudo-globulin occupies an intermediate position. This may explain the fact that the serum of certain horses is more liable to cause a serum disease than the serum of other horses.

Muir and Ritchie⁹ lay stress on the development of a reaction body or antiserum - probably each of the serum proteins are capable of exciting a precipitin formation and that the precipitin obtained in each case reacted most strongly with the protein used in its production. They state that the serum antigens gradually disappear from the body after the injection. From about the 8th day onwards, anti-substances appear in the blood in large amount and if the/

the antigens are still present in the proper amount the combination of the two probably acted on by complement brings about the phenomenon. If on the other hand antigens have disappeared before the anti-substances appear in quantity there will be no symptoms. At a later period antisustances will be present alone in the serum and then the injection of fresh antigens brings about an immediate reaction. After the anti-substances have disappeared the injection of fresh serum causes no immediate reaction but the mechanism of reaction has been stimulated by the first injection; antisustances then appear more quickly after the second injection, hence the reaction is "accelerated" as compared with the reaction after the first injection.

It is thus seen that each of the three proteins can act as an anaphylactic antigen; each is capable of exciting precipitin formation in the blood.

It was also noted that the percentage of serum rashes with the use of concentrated serum was much less than with the unconcentrated. This can be explained by the fact that concentration of the serum largely removes the euglobulin and albumin part, whereas the pseudo-globulin remains. As it was already stated that the experiments of Ledingham proved that the euglobulin presented the maximum anaphylactic activity, this reasoning, therefore, seems perfectly feasible.

S U M M A R Y.

The information obtained from the foregoing study of serum disease is of great importance and may now be summarised as follows.-

1. Serum disease occurred either in the form of an immediate or an accelerated reaction. Much the same symptoms were observed in both cases but in the accelerated reaction the incubation period was shortened and the whole process was more rapid, with more acute symptoms.
2. As the disease followed the administration of antistreptococcal and antitetanic serum as well as antidiphtheritic, the phenomena was found to be due to the serum itself or the protein non-antitoxic part of the serum and not to the antitoxic part.
3. Four distinct varieties of serum disease were observed, namely, multiform, erythematous, urticarial, morbilliform, and scarlatiniform. These four differed from each other not only in the type, order of occurrence, period of incubation/

incubation and duration of their rashes, but also in the frequency of occurrence of the other symptoms of serum disease as pyrexia, arthritis, etc., and in the degree of severity of those symptoms and also certain features common to the varieties differed greatly in degree.

4. The commonest type of rash met with was the multiform erythematous, then the urticarial, the morbilliform and the scarlatiniform in that order of frequency, but on the whole the morbilliform variety was noted as the severest form, then the multiform, urticarial and scarlatiniform in that order of severity.
5. The cases that developed two rashes were observed to have a primary rash in all cases of the urticarial type; while the secondary rash in two of the cases was a multiform type and in one of the cases a morbilliform type, the explanation of the two rashes in one person no doubt being the mixing of the sera of two or more horses and the character of the rash largely depending on the idiosyncrasy of the horse.
6. The four varieties also presented a different blood picture and while a leucopenia was observed in/

in a certain percentage of all the varieties, yet a greater percentage of the multiform and morbilliform types showed a greater leucopenia than the urticarial and scarlatiniform types.

The relatively increased proportion of lymphocytes to polymorphonuclear leucocytes again was noted in the same order of occurrence of the different varieties.

The cases presenting a relative increase in the numbers of eosinophils were found to have a history of asthma and this must be taken as the explanation meantime until further investigations are carried out.

The theoretical cause of this disturbance of the balance between lymphocytes and polymorphonuclear leucocytes was taken as the results of certain reactions on the part of the blood forming tissues produced by the actions of certain toxic substances either from the action of the proteins of horse serum or by poisons generated by perverted metabolic processes within the tissues and the organs of the patient himself.

7. There is no doubt that the four varieties though similar in a general way; yet are distinct and independent/

independent and probably produced by different causes - different sera producing different sera phenomena. Just as the four varieties show a general similarity; it is possible that the causes show a general similarity, yet have an independent action and a separate existence.

8. The amount of each protein - euglobulin, pseudoglobulin and albumin - present in horse serum is a variable quantity and there may be considerable preponderance of one over the other; thus accounting for the fact that the serum of certain horses is more liable to cause serum disease than the serum of other horses.

Each of the three proteins is capable of exciting or producing precipitin or antistubstance formation in the blood in serum disease and is found to disappear from the blood during the course of the disease.

9. Concentration of the serum involves removal of the euglobulin factor and as this was noted to contain the maximum anaphylactic activity consequently the percentage of serum rashes with the use of concentrated serum was much less than with the unconcentrated.

10. Serum disease was observed to be closely related to anaphylaxis; which depends on the introduction into the body of a foreign protein and on the production of a poisonous substance produced by the reaction between the body cells and the cleavage products of the foreign protein. The symptoms also, it was observed, were not quite those of serum disease yet they were essentially the same and differed only in degree of intensity.

The results of this investigation have been an attempt to co-relate the various types of serum disease with observations on their various symptoms and blood features, with the action of the proteins of horse serum on the human tissues, and the relationship of the actions of those proteins to anaphylactic reactions.

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